Exposure to Metal Ions and Susceptibility to Dental Caries

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Abstract:

Results from several epidemiologic studies have shown that there are large differences in the prevalence of dental caries from one region to another within the United States as well as in other countries. It has been postulated that the observed differences may be attributed in part at least to exposure to trace elements such as selenium, vanadium, molybdenum, strontium, and lead. Although data from epidemiologic studies usually support this hypothesis, direct evidence is sparse with the possible exception of exposure to lead. Data from several epidemiologic studies and animal based research support the concept that lead is a caries promoting element. Lead mimics calcium in several respects and may affect development of teeth and salivary glands, clearly enhancing susceptibility to dental caries. Elevated blood levels are found most commonly in persons residing in inner cities, particularly among the poor. Many states require blood lead level to be monitored in young children. Where feasible these records should form part of health history and be available to the treating dental practitioner to ensure that extra preventive procedures may be implemented.

Keywords: lead, enamel, caries

There are large variations in the prevalence of dental caries from one region to another in the United States. Every national and regional survey of the prevalence of dental caries in children and in adults supports these observations.[1-4] Less clear, however, are the reasons for these regional variations. For example, it is unclear whether the disparities observed can be attributed to enhanced resistance or increased susceptibility. Several hypotheses have been advanced to explain the phenomena ranging from exposure to trace metals, level of rainfall, hours of sunshine, to dietary practices. It is well recognized that geological conditions (soil and water) vary enormously from area to area although the general opinion (with few exceptions) is water is not a major source of trace metals.[5,6]

The inadvertent ingestion of specific metals, in particular lead, has been recognized as constituting a major hazard to health for decades. Indeed, high blood lead levels are among the most prevalent childhood conditions and the most prevalent environmental threats to the health of children in the United States.[7]

Few organ systems appear to escape its adverse effects,[8] although most attention has been focused on decreased intelligence and impaired neurobehavioral development in children and adolescents.[9] There are significant risks of toxicity even where individual sources of lead are low, because all sources of lead are integrated systemically into critical target tissues.[10] The margin of safety with lead is very narrow. The Centers for Disease Control has lowered the acceptable concentration of lead in blood in young children from < 25 to < 10 ug/dL.[11] Some investigators regard even this level to be more than 600 times higher than the natural levels of lead in humans.[12]

The adverse effects of lead on the oral tissues have been noted for many centuries. For example, Nikander (Greek poet: 2nd century B.C.), cited by Landrigan[8] noted regarding ingestion of cerusa (lead carbonate):

"The mouth it inflames and makes cold from within
The gums dry and wrinkled are parched like the skin
The rough tongue feels harsher the neck muscles grip
He soon cannot swallow foam runs from, his lip…"

Ramazzine (1713) also cited by Landrigan[8] writing on lead poisoning, noted "First their hands become palsied, then they become paralytic, splenetic, lethargic and toothless."

The number of children at risk for developing lead poisoning is enormous, particularly impoverished children who live in inner cities.[13] About 14 million or more children less than seven years of age are at enhanced risk because they reside in housing built before 1960.[14,15] These houses harbor the highest concentrations of lead paint. At least twenty million houses have peeling lead-based paint; approximately four million of these homes are occupied by families with children under seven years of age. Collectively, therefore, it is estimated by the Centers for Disease Control[16] that 890,000 (4.4%) of children in the USA aged one to five years have elevated levels of lead in their blood (≥ 10 ug/dL) (BLL). The prevalence of elevated BLLs was found to be 5.9 percent among children aged one to two years; in older children (3-5 years) the prevalence was 3.5 percent. Non Hispanic black children (21.9%) and Mexican American children (13.0%) particularly those living in older housing appear to be particularly prone. It must be emphasized that the risks of lead toxicity are not limited to post-natal exposure. Lead readily crosses the placenta and can affect the development and maturation of several organ systems.[17,18] Women of childbearing age represent between 40 percent and 50 percent of the

total female population; it is estimated that approximately 4,460,000 residing in urban populations have blood levels (>10 ug/dL) that could impair healthy fetal development. Approximately 9 percent of these women are pregnant at any one time; therefore about 400,000 pregnancies are at risk for adverse health effects from maternal lead in any given year.[19,20] Clearly, for example, over a ten year period, unless significant efforts are made to abate pollution by lead, ten times that number of fetuses will have been exposed to the harmful effects of lead. Because of mobilization of lead from bone during pregnancy, transfer of lead to fetus is likely to be enhanced. In addition, it has been observed that older women secrete more lead in their milk than do younger women, levels ranging from 0.24-35 ug/dL have been reported.[21]

Although there has been some lowering of blood lead levels in some segments of the population during recent years, blood lead levels continue to be of concern to African Americans, central city residents, residents in the Northeast region of the United States, persons with low income and those with low educational attainment.[16,22] It is interesting to note that these are the persons and the regions where the highest prevalences of caries are observed.

Blood levels of lead give a clear indication of current exposure to lead; however, they do not necessarily accurately reflect the historic exposure to lead. Because lead mimics the effects of calcium in several respects, it is readily incorporated in calcifying tissues.[23,24] Enamel and dentine are usually not subject to significant remodeling, the levels of lead in these tissues (particularly circumpulpal dentine) are frequently measured to assess children's exposure to lead.[25,26] Indeed, Needleman et al.'s study associating lead with deficits in psychologic and classroom performance in children, used lead levels in dentine as evidence of exposure.[9]

THEORETICAL BASES OF HOW EXPOSURE TO LEAD COULD ENHANCE SUSCEPTIBILITY TO CARIES

There are several possible mechanisms through which lead could enhance susceptibility to caries. Information on the effect of lead on enamel and dentine formation is sparse, even though considerable information has accumulated on lead concentrations in deciduous teeth in various communities. Furthermore, the relationship between lead in blood and that in dentine has been explored.[27]

Lead ions apparently act directly on bone mineral to replace calcium and phosphorus in the crystal lattice and induce a hypercalcemia and a hyperphosphatemia.[28] The incidence of enamel hypoplasia is increased in children and animals exposed to elevated levels of lead.[28-30] A "lead line" was noted by Appleton in the continuously erupting incisors of rats following a single injection of a large dose of lead acetate.[28] Further examination of this line revealed irregular tubular structures and uneven mineralization probably as a result of incomplete fusion of small calcospherites. These observations suggest that lead may affect odontoblast function and thereby influence dentine formation. Support for this concept is found in the comprehensive review by Pounds, Lang and Rosen who show that lead intoxication directly and indirectly alters many aspects of bone cell function.[24] Lead alters bone cell function through changes in 1,2,5 dehydroxyvitamin D3; it may perturb ability of cells to respond to hormonal regulation. Lead may impair ability of cells to synthesize collagen or bone sialoproteins and lead may directly affect or substitute for calcium in the active sites of the calcium and cAMP messenger systems. Furthermore Kato, Takimoto and Ogura suggest that lead may have a direct effect on the mineral phase of calcifying tissues.[29] It has been postulated that lead may first adsorb to hydroxyapatite crystals and later take positions within the structure.[31,32] Featherstone, Nelson, and McLean

observed wide dispersal of lead by means of electron microscopy when Pb hydroxyapatite is formed synthetically.[33] Studies carried out *in vitro*[34] using synthetic apatite crystals show that replacement of calcium by lead is a slow process; however, in a dynamic mineralizing system clearly lead can be incorporated into apatite rapidly, as shown by enhanced levels of lead in enamel and dentine of children ingesting elevated levels of lead. Results from studies conducted by Grobler et al. showed that airborne lead is absorbed by rats and incorporated into developing enamel and further that blood lead can become supplemented after direct exposure has ceased through mobilization from alveolar bone, as has been reported for other bones.[35]

Levels of lead as high as 4000 ppm have been found in the outer layers of enamel.[36,37] Because of the possibility of enamel acquiring lead post-eruptively particularly in contaminated environments, many investigators have used lead in dentine to determine exposure to this element.[27] Using this approach Bercovitz and Laufer examined impacted teeth to determine the absorption of lead into the body.[38] They concluded that lead accumulates during formation of the dental tissues; clearly, because lead readily crosses the placenta, lead accumulates in the developing deciduous teeth.[17] Presence of lead in the environment may also affect adversely the development and function of the salivary glands. For example, rat salivary glands begin to develop at approximately embryonic day 15.[39] Parasympathetic innervation precedes sympathetic innervation during the late prenatal period.[40] Both sympathetic[41-43] and parasympathetic[44] denervation retards gland development. Lead is known to produce peripheral neuropathies such as slower maturation of synaptic density,[45] reduction in conduction rates[46,47] and depression of pre-synaptic release of acetylcholine in the superior cervical ganglion.[48,49] Many of the effects of lead on the peripheral nervous system are apparently associated with its ability to inhibit Ca^{2+} uptake.[49,50] Clearly perinatal exposure to lead could produce long-lasting

influence on salivary function by interfering with normal autonomic nervous system-salivary gland interactions during development.

Lead also may act directly on gland tissue to inhibit saliva formation. Heavy metals, in particular lead, interfere with normal Ca^{2+} metabolism, acutely altering normal cell function.[51,23,52] Perturbation of Ca^{2+} metabolism has severe consequences on salivary gland function; therefore, one of the most likely mechanisms by which lead may acutely interfere with saliva formation is its interaction with Ca^{2+} metabolism. Available evidence, sparse as it is, clearly shows that administration of lead results in significantly (30-40%) diminished stimulated salivary flow rates in rats.[53,54] The phenomenon has not been examined in humans.

Lead appears to be concentrated in dental plaque, that is, significantly more per unit is found there than in the surrounding saliva. For example, levels of 2·7 ppm up to 54·7 ppm were reported in dental plaque by Schamschula and Bunzel,[55] Beighton et al.[56] It is worthy of note that in one study elevated levels of lead in plaque were associated with increased prevalence of caries.[57]

Thus based on available data, there is good, credible evidence that ingestion of lead hypothetically at least could influence susceptibility to dental caries.

PRESENT STUDY OBJECTIVES

Although there is much objective evidence for the role of many trace elements in the etiology of dental caries, the quality of the evidence rarely meets current epidemiological or experimental standards.[58] Frequently objective measurements of exposure to the element of interest is lacking. I have chosen to focus on lead because I consider it the only one for which

human exposure can be readily documented and appropriate action by the dental practitioner may be implemented.

Clearly when exploring the published data it would have been unrealistic to expect to have found controlled clinical studies determining the effect of lead on caries in humans. Much of the data supporting a role for lead in the etiology of caries comes from results of epidemiologic studies which understandably vary in quality. In addition, significant data have been gleaned from animal studies which clarify the role of lead in the etiology of dental caries.

LITERATURE SEARCH

I conducted detailed researches of the English language literature from 1960 to January 2001 using MEDLINE. This is proved to be more difficult than anticipated because the word lead (which occurs frequently in titles) can be confused with the metallic element "Lead." In addition, I searched the so-called gray literature which included old textbooks.[5,59,60] I also searched these from the University of Rochester, Rochester, NY.

SELECTION CRITERIA

I included those studies conducted on humans only where the prevalence of caries was determined and in addition where a determination of exposure to lead could be confirmed. In three papers we were unable to determine how a study was conducted or a simple statement was made without data. These were excluded.

I found 22,950 references to “dental caries,” 7,806 to “trace elements,” 851 to “trace metals & caries.” Search for “Lead” revealed 111,268 (see above). “Dental plaque” yielded 10,658. Combination of “dental caries” and “lead” yielded 118; “dental caries “ and “trace elements” 71. All of these were examined for their relevance to current review.

In the animal based studies (exclusively rats and hamsters) we included only those studies where lead was included in diet and/or drinking water. Studies for example of the topical application of lead fluoride were not included.

RESULTS

The epidemiologic studies varied considerably in the methods used to determine exposure to lead. Of the 12 studies (Table 1) we have included, in four, the relationship of caries prevalence has been correlated with lead levels in soil/water. Clearly the approach is less than completely satisfactory; analyses of enamel, plaque blood or other tissues would have offered supporting and confirmatory evidence that subjects did indeed ingest lead. In five instances, lead was measured in teeth and even there different and distinct approaches were used. In one, an enamel biopsy was used: in the course of this study it was shown that the level of lead declines from surface to the enamel-dentin junction. An additional study used whole enamel as source and as expected, levels of lead were dramatically lower than those found in teeth whose surface enamel was biopsied. In three studies whole teeth were used. In two studies, levels of lead in blood were determined. Clearly blood levels were measured sometime after tooth development; nevertheless, it is generally accepted that blood levels detected in the first years of life are indicative of longer term exposure.

The methods used to measure the prevalence of caries also as expected varied from study to study. In some instances[61] there was probably underreporting because frank cavitation only was recorded.

Some of the studies warrant special comment. The two studies conducted by Anderson, Davies and James,[62] Anderson and Davies,[63] Anderson et al.[64] in the same area of Wales ten years apart yielded different results. It is unclear that the same level of pollution existed over the ten-year period. In addition, it is particularly noteworthy that the prevalence of DMFT declined by over 50 percent in the same age groups over the ten-year span.

Most of the studies included comparatively few subjects with the obvious exception of the Moss et al. data.[65] They used data from the NHANES III collected from 1988 to 1994, and suggest "the population attributable risk of lead exposure is estimated to be 13.5 percent of dental caries among individuals exposed to the highest age-specific textile of lead level." They further state that their "data further indicate that approximately 2.7 million excess cases of dental caries in older children and adolescents may be attributable to environmental lead exposure itself or a factor that is directly linked to environmental lead exposure."

The study conducted by Campbell, Moss and Raubertas also merits comment; it is one of a couple that failed to show a relationship between ingestion of lead and prevalence of caries.[66] It is, however, important to emphasize the statement made by the authors, i.e. that "the study lacked statistical power to demonstrate statistical significant correlations."

I detected just one animal study where lead was administered throughout gestation. The resulting data show clearly that the susceptibility of rats exposed to lead pre and perinatally is enhanced by close to 40 percent. No evidence is available which demonstrates that exposure to lead post-eruptively has any effect on the incidence of carious lesions.

COMMENTS

Clearly epidemiologic studies on their own provide less than completely satisfactory evidence. The studies cited here provide an additional problem in that the source of lead to which correlations of caries prevalence are made, vary greatly. The best evidence of lead exposure is clearly analyses of lead in enamel; blood lead levels in children also provide excellent evidence of exposure but there is also some uncertainty on whether it was elevated during tooth formation.

Somewhat surprisingly few well-controlled animal studies have been carried out. The study of Wisotzky and Hein (Table 2) in hamsters showed that ingestion of lead post-eruptively promoted development of caries but only in male animals; [67] a puzzling result: the study by Watson et al.[54] provides clear and unequivocal evidence of the influence of pre and peri-natal exposure on caries susceptibility in rats. Furthermore, the model represents the situation which prevails in inner cities where young females grow in a lead-polluted environment. As a result, when these women are pregnant, their fetus is exposed to lead released from its mother's skeletal system and of course continuous exposure to lead from the environment.

Clearly no single study on its own provides unequivocal proof that exposure to lead is caries promoting, nevertheless when the pattern of the epidemiological studies is examined, combined with the data from animals, one is inevitably drawn to the conclusion that lead does indeed enhance the susceptibility to dental caries.

IMPLICATIONS FOR DENTAL PRACTITIONER

Superficially it may appear that once lead has been incorporated into enamel that little can be accomplished towards alleviating its adverse effects. Clearly enamel biopsies are difficult and cumbersome for a practitioner to conduct, and certainly are not part of routine practice. However, the determination of levels of lead in blood of very young children is now a routine procedure and is required by law in several states, indeed many states receive funds from the Centers for Disease Control to develop surveillance systems. Clearly it would be highly desirable to have such information as part of patient clinical dental records. The practitioner may then implement extra preventive procedures appropriate for enhanced risk.

The most impoverished in society (Medicaid recipients) show the highest prevalence of elevated blood lead levels during childhood. Medicaid accounts for 60 percent of all children, aged one to five years who have elevated blood levels. Unfortunately the recipients screening rates are deplorably low in Medicaid children.[16] Nevertheless by eliciting a history of lead exposure the practitioner can enhance the public's awareness of the many adverse consequences of lead exposure.

NEED FOR ADDITIONAL RESEARCH

All the available data show very clearly large disparities in the prevalence of dental caries from region to region and even within regions. These differences have persisted even when the incidence of dental caries has declined following introduction of fluorides. There have been few

systematic studies to explore these important phenomena. The differences observed frequently exceed those recorded following use of our most successful therapeutic agents.

Lead is but one of many elements that apparently has an influence on caries.[5,68,69] The mechanism of action of lead in increasing susceptibility to caries is not completely solved, even though there appears to be a sound rationale to explain its effects and the unraveling of this mystery could provide insights into, for example, "caries susceptible teeth."

Research into relationship trace metals, e.g. selenium, molybdenum, vanadium, strontium and dental caries has in the past focussed largely on the effect these may have on hard tissues; their possible effects on plaque formation, plaque metabolism has to a large extent gone unexplored.

Many trace elements work in concert with each other for example copper and molybdenum; fluoride and aluminum may also interact. Many of the studies of trace elements have involved investigating the effects of a single element, which may overlook important interactions. Clearly this whole area of research is rich in promise and could be enormously rewarding.

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Table 1: Summary of Epidemiologic Studies

YEAR	AUTHOR	POPULATION	NUMBER OF SUBJECTS	AGE	LEAD SOURCE	DMFS(T)	CORRELATION	STATS
1969	Barmes (61)	Sepik River	702	4-45	Soil/Food	+(T)	+	+
1970	Ludwig (6)	19 Town USA		12-14	Drinking Water	+(T)	+	+
1976	Anderson et al. (62)	West England	171	12	Soil	+(T)	+	+
1977	Brudevold et al. (36)	Cambridge, MA	251	9-12	Enamel Biopsy	+(S+T)	+	+
1978	Curzon & Crocker (69)	USA & New Zealand	337	10-20	Whole Enamel	+(T)	0	+
1980*	Anderson & Davies (63)	Wales	186	12	Soil/Water	+(T)	+	+
1986*	Anderson et al. (64)	Wales	279	12	Soil/Water	+(T)	0	+
1994	Sood & McDonald (70)	England	54	?	Whole Teeth	+(T)	+	+
1994[+]	Gil et al. (71)	Spain	?	10-60+	Whole Teeth	--	0	--
1996[+]	Gil et al. (72)	Spain	?	10-60+	Whole Teeth	DMF(T)	+	+
1999	Moss et al. (65)	USA	24,901	2-11	Blood	DMFS	+	+
2000	Campbell et al. (66)	USA	248	8-11	Blood	dmfs DMFS	0	+

- ***Same areas re-examined after 10 years.**
- **[+] Appears to be same populations.**

Table 2: Summary of Animal Studies

YEAR	AUTHOR	SPECIES	NUMBER OF ANIMALS	SOURCE OF LEAD	PRENATAL	POSTNATAL	CARIES PROMOTING	STATS
1958	Wisotzky & Hein (67)	Hamster	10-12	0.5 millequiv as lead acetate in water	No	+	+ Males Only	+
1997	Watson et al. (54)	Rats	136	34 ppM Pb as acetate in water	Yes	Up to weaning	+	+
1999	Tabchoury et al. (73)	Rats	48	10 ppM Pb or 25 ppM Pb as acetate in water	No	+	No Effect	+